PATENT
1718-0220PUS1

IN THE U.S. PATENT AND TRADEMARK OFFICE

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| Applicant: | ANTONOV, Dmitry et al | Conf.: | 7502 |
| Appl. No.: | 10/526,598 | Group: | 1623 |
| Filed: | March 4 2005 | Examiner: | Olson, Eric S |
| For: | NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS | | |

**DECLARATION SUBMITTED UNDER 37 C.F.R. § 1.132**

Honorable Commissioner
Of Patents and Trademarks
Washington, D.C. 20231

July 16, 2008

Sir:

I, Dr. Christer Sahlberg, Lunastigen 7, 141 44 Huddinge, Sweden, do hereby declare the following:

I have the degrees of M.Pharm and PhD awarded by Uppsala University.

I have been an associate professor of the Department of Organic Pharmaceutical Chemistry, Uppsala University since 1989.

I have worked with the development of antiviral drugs, notably against HIV, since 1987. This has included senior positions in the Antiviral Laboratory at Astra AB, Södertälje, Sweden during the period 1987-1988, and as senior scientist and research fellow with the present assignee Medivir AB since that time.

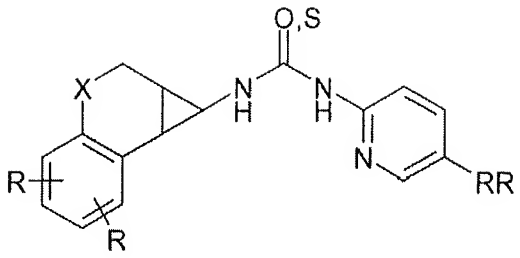
I am author or co-author of many academic articles, posters and conference presentations in the field of HIV antiviral drugs including publications in peer-reviewed journals such as Journal of Medicinal Chemistry, Antiviral Research, European Journal of Biochemistry, and Biorganic and Medicinal Chemistry Letters. I am designated as inventor in approximately 8 international patent applications relating to HIV antivirals.

During the development of the presently claimed compounds, I was project director for Medivir's non-nucleoside reverse transcriptase inhibitor project. I am an inventor of record for the above-captioned patent application. Thus I am well acquainted with these compounds and the background research behind their development.

I am familiar with the above referenced patent application and the Office Action of 10 April 2008.

The following comments are offered in support of the patentability of the invention embodied in US patent application no. 10/526,598.

The present compounds are a further development of the tricyclic urea and thiourea non-nucleoside reverse transcriptases inhibitors (NNRTIs) described and claimed in Medivir's US patent nos. 6,610,714 and 6,716,850. A favoured group of compounds envisaged in these patents has the formula




where X is O or methylene, the left-most ring is diversely substituted and the RR group on the rightmost ring is a small polar substituent such as halo or cyano.

US patent 6,716,850 also discloses a small number of compounds which deviate from this pattern, in that they employ alternative heterocycles to the above depicted pyrid-2-yl. The patent also discloses a further compound which does possess the pyrid-2-yl ring depicted above, but deviates from the general pattern in that RR is a phenoxy group. In particular Example 20 of US 6,716,850 discloses the compound denoted +/- *cis*-1-(4,7-difluoro-1,1a,2,7b-tetrahydro-cyclopropa[c]chromen-1-yl)-3-(5-phenoxy-pyridin-2-yl)-urea: with the formula:

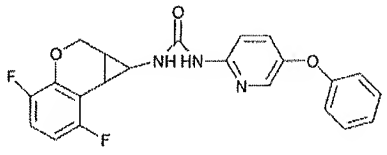
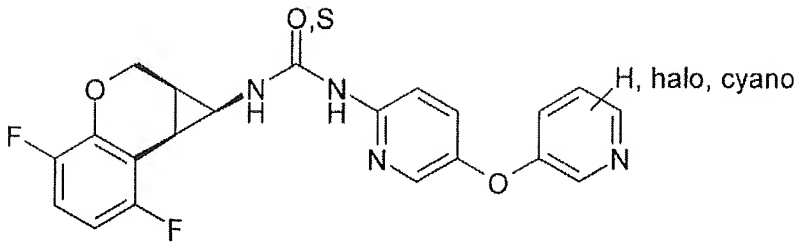



Table 1 of the '850 patent indicates that the Example 20 compound has an $ED_{50}$ of 7 nM against the wild type $HIV\text{-}1_{IIIB}$ in a conventional XTT cell culture assay.

I understand that the claims in the present patent application are being amended contemporaneously with this declaration to focus on compounds of the formula:




Based on the performance of the above described Example 20 of the '850 patent, which I consider to be the closest compound to the compounds of the revised claims in the present application, we expected that the present pyrid-3-yloxy compounds ought reasonably to be active (at least against the wild type HIV) and to about the same degree as the Example 20 compound.We did not expect to see the unusually profound levels of activity against problematic HIV drug escape mutants exhibited by the compounds now claimed in the present application.

We have tested Example 20 of the '850 patent and representative compounds of the presently amended claims in XTT-based cell culture assays using HIV strains bearing characteristic drug escape mutants in the reverse transcriptase gene.

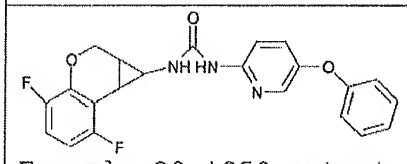
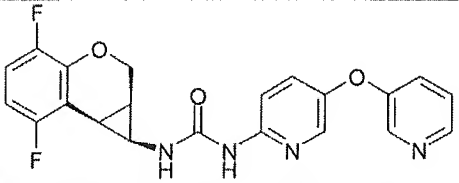
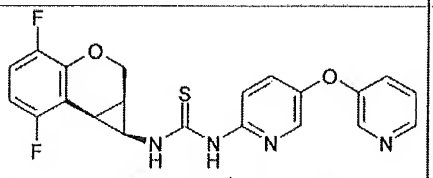
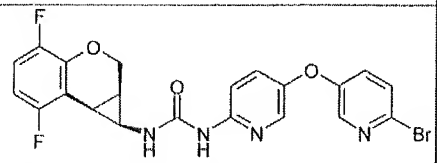
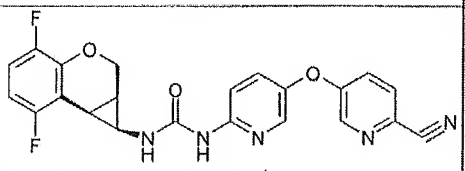
The meaning and significance of drug escape mutants is illuminated in the present patent application, but in short, a drug escape mutant is a viral strain which is selected by the antiviral pressure exerted by administration of currently marketed antiretroviral drugs. Each class of antiretrovirals, such as nucleosides or protease inhibitors, tends to select characteristic patterns of mutations in the target enzyme which help the respective mutants to evade that antiviral pressure. In the case of NNRTIs, key drug escape mutants selected by currently marketed drugs, such as efavirenz (Sustiva®), include L100I, K103N and/or Y181C.

As presented in the attached table, Example 20 of the '850 patent has an $ED_{50}$ of 170 nM for HIV virus bearing drug escape mutations at position 181, an $ED_{50}$ of 23 nM for

HIV virus bearing drug escape mutations at position 103 and an $ED_{50}$ of 3 uM for HIV virus bearing a drug escape double mutation at positions 100 and 103a. In contrast, the compound of Example 85 of the present application has $ED_{50}$s of 5.9 nM, 5.2 nM and 0.18uM against these same mutants. In other words the compound of present Example 85 is 29-fold more potent that '850 Example 20 with the 181 mutant, 4.4-fold more potent against the 103 mutant and 16.6-fold more potent against the double mutant 100/103.

Differences in susceptibility of this order of magnitude are highly unexpected and of tremendous significance in the clinical application of the drugs.

It will be seen from Table 1, that other compounds within the presently amended claims are also consistently much better against problematic drug escape mutants than Example 20 of the '850 patent, although naturally the fold-changes vary a little from compound to compound.

| | HIV-1 strain: characteristic RT drug escape mutation | | |
|---|---|---|---|
| | Y181C | K103N | L100I & K103N |
|  Example 20 '850 patent | 170 nM | 23 nM | 3000 nM |
|  Example 43A US 10/526,598 | 9.8 nM | 15.5 nM | 950 nM |
|  Example 43 US 10/526,598 | <3.2 nM | 9.8 nM | 830 nM |
|  Example 84 US 10/526,598 | 35 nM | 8.8 nM | 870 nM |
|  Example 85 US 10/526,598 | 5.9 nM | 5.2 nM | 180 nM |

The undersigned hereby declares that all statements made herein based upon knowledge are true, and that all statements made based upon information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements may jeopardize the validity of the application or any patent issued thereon.

DATED: 16 07 2008 Christer Sa

Dr. Christer Sahlberg